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☐ 1. Document ID: US 6022540 A

L2: Entry 1 of 5 File: USPT Feb 8, 2000

US-PAT-NO: 6022540
DOCUMENT-IDENTIFIER: US 6022540 A
TITLE: Ligands that modulate differentiation of mesenchymal stem cells

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 5981483 A

L2: Entry 2 of 5 File: USPT Nov 9, 1999

US-PAT-NO: 5981483
DOCUMENT-IDENTIFIER: US 5981483 A
TITLE: Compositions comprising modulators of cytokines of the TGF-.beta. superfamily

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 5866098 A

L2: Entry 3 of 5 File: USPT Feb 2, 1999

US-PAT-NO: 5866098
DOCUMENT-IDENTIFIER: US 5866098 A
TITLE: Assay for identifying extracellular signaling proteins

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 4. Document ID: US 5585087 A

L2: Entry 4 of 5 File: USPT Dec 17, 1996

US-PAT-NO: 5585087
DOCUMENT-IDENTIFIER: US 5585087 A
TITLE: Assay for identifying extracellular signaling proteins

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

5. Document ID: AU 9944098 A, WO 9961044 A1
L2: Entry 5 of 5 File: DWPI Dec 13, 1999

DERWENT-ACC-NO: 2000-062583
DERWENT-WEEK: 200020

TITLE: Regulating bone resorption, density and remodeling, using an antagonist of bone morphogenic protein, or antibody to the antagonist

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Term	Documents
BMP.DWPI,EPAB,JPAB,USPT.	1378
BMPS.DWPI,EPAB,JPAB,USPT.	292
BONE.DWPI,EPAB,JPAB,USPT.	85456
BONES.DWPI,EPAB,JPAB,USPT.	19991
MORPHOGENIC.DWPI,EPAB,JPAB,USPT.	903
MORPHOGENICS.DWPI,EPAB,JPAB,USPT.	1
PROTEIN.DWPI,EPAB,JPAB,USPT.	187511
PROTEINS.DWPI,EPAB,JPAB,USPT.	108186
CELL.DWPI,EPAB,JPAB,USPT.	652328
CELLS.DWPI,EPAB,JPAB,USPT.	432245
(BMP AND (BONE MORPHOGENIC PROTEIN) AND CELL AND CULTURE AND (FETUIN OR NOGGIN OR CHORDIN OR GREMLIN OR FOLLISTATIN)).USPT,JPAB,EPAB,DWPI.	5

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Establishment and maintenance of the border of the **neural** plate in the chick: involvement of FGF and **BMP** activity.
Streit A; Stern CD
Department of Genetics and Development, Columbia University, 701 West 168th Street, New York, NY 10032, USA.
Mechanisms of development (IRELAND) Apr 1999, 82 (1-2) p51-66, ISSN 0925-4773 Journal Code: AXF
Contract/Grant No.: HD31942, HD, NICHD; GM53456, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have investigated the cell interactions and signalling molecules involved in setting up and maintaining the border between the **neural** plate and the adjacent non-**neural** ectoderm in the chick embryo at primitive streak stages. msx-1, a target of **BMP** signalling, is expressed in this border at a very early stage. It is induced by FGF and by signals from the organizer, Hensen's node. The node also induces a ring of **BMP** -4, some distance away. By the early neurula stage, the edge of the **neural** plate is the only major site of **BMP**-4 and msx-1 expression, and is also the only site that responds to **BMP** inhibition or overexpression. At this time, the **neural** plate appears to have a low level of **BMP** antagonist activity. Using in vivo grafts and in vitro assays, we show that the position of the border is further maintained by interactions between non-**neural** and **neural** ectoderm. We conclude that the border develops by integration of signals from the organizer, the developing **neural** plate, the paraxial mesoderm and the non-**neural** epiblast, involving FGFs, BMPs and their inhibitors. We suggest that BMPs act in an autocrine way to maintain the border state.

5/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09925594 99262105
Functional analysis of human Smad1: role of the amino-terminal domain.
Xu RH; Lechleider RJ; Shih HM; Hao CF; Sredni D; Roberts AB; Kung Hf
Intramural Research Support Program, SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Developmental Center, Frederick, Maryland 21702, USA. xur@mail.ncifcrf.gov
Biochemical and biophysical research communications (UNITED STATES) May 10 1999, 258 (2) p366-73, ISSN 0006-291X Journal Code: 9Y8
Contract/Grant No.: NO1-CO-56000, CO, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The signals originating from transforming growth factor beta/activin/bone morphogenetic proteins (BMPs) are transduced by a set of evolutionarily conserved family of Smad proteins which, upon activation, directly translocate to the nucleus where they may activate transcription. Smad proteins of different species contain conserved amino- (N) and carboxy- (C) terminal domains separated by a proline-rich linker. Human, Drosophila, and Xenopus Smad1 all have been shown to mediate the biological effects of **BMP**-4 in Xenopus embryos. We have investigated the functional domains of human Smad1 (hSmad1) using the Xenopus embryo system. Dorsal injection of hSmad1 RNA into the 4-cell-stage embryos results in embryonic ventralization. Since the C-terminus of Smads has been shown to mediate the transcriptional activity, whereas this activity is masked by the presence of the N-terminus, we tested the effect of a hSmad1 construct lacking the C-terminal domain [hSmad1(N)] in the Xenopus embryo system. Surprisingly, we found that hSmad1(N) not only synergizes with hSmad1 in embryonic ventralization, but induces ventralization by itself. Ectopic expression of a dominant negative **BMP** receptor (DN-BR) as well as **neural** inducers **noggin** and **chordin** induce neurogenesis in the animal cap, which is inhibited by co-expression of either hSmad1 or hSmad1(N). Ventral expression of DN-BR induces formation of a second body axis at tailbud stage, which is also prevented by hSmad1 and hSmad1(N). It has

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? s bone morphogenic protein or bmp

             59  BONE MORPHOGENIC PROTEIN
           3551  BMP
      S1   3583  BONE MORPHOGENIC PROTEIN OR BMP
? s s1 and (neuron or neural)

           3583  S1
          92654  NEURON
         666911  NEURAL
      S2    507  S1 AND (NEURON OR NEURAL)
? s s2 and (fetuin or noggin or chordin or gremlin or follistatin)

            507  S2
           2295  FETUIN
            518  NOGGIN
            306  CHORDIN
             33  GREMLIN
           1179  FOLLISTATIN
      S3    148  S2 AND (FETUIN OR NOGGIN OR CHORDIN OR GREMLIN OR
                 FOLLISTATIN)
? s s3 and cell

            148  S3
        3294001  CELL
      S4     74  S3 AND CELL
? rd s3

...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
      S5     89  RD S3 (unique items)
? t s5/3,ab/all


 5/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10556397   20302575
  Expression of Crim1 during murine ocular development.
  Lovicu FJ; Kolle G; Yamada T; Little MH; McAvoy JW
  Department of Anatomy and Histology, The University of Sydney, Australia.
lovicu@anatomy.usyd.edu.au
  Mechanisms of development (IRELAND)  Jun 2000,  94 (1-2) p261-5,  ISSN
0925-4773   Journal Code: AXF
  Contract/Grant No.: EY03177, EY, NEI
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  Crim1 (cysteine-rich motor neuron 1), a novel gene encoding a
putative transmembrane protein, has recently been isolated and
characterized (Kolle, G., Georgas, K., Holmes, G.P., Little, M.H., Yamada,
T., 2000. CRIM1, a novel gene encoding a cysteine-rich repeat protein, is
developmentally regulated and implicated in vertebrate CNS development and
organogenesis. Mech. Dev. 90, 181-193). Crim1 contains an IGF-binding
protein motif and multiple cysteine-rich repeats, analogous to those of
chordin and short gastrulation (sog) proteins that associate with
TGFbeta superfamily members, namely Bone Morphogenic Protein (BMP).
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High levels of Crim1 have been detected in the brain, spinal chord and lens. As members of the [redacted] and TGFbeta growth factor fa[redacted]ies have been shown to influence the behaviour of lens cells (Chamberlain, C.G., McAvoy, J. W., 1997. Fibre differentiation and polarity in the mammalian lens: a key role for FGF. Prog. Ret. Eye Res. 16, 443-478; de Iongh R.U., Lovicu, F.J., Overbeek, P.A., Schneider, M.D., McAvoy J.W., 1999. TGF-beta signalling is essential for terminal differentiation of lens fibre cells. Invest. Ophthalmol. Vis. Sci. 40, S561), to further understand the role of Crim1 in the lens, its expression during ocular morphogenesis and growth is investigated. Using in situ hybridisation, the expression patterns of Crim1 are determined in murine eyes from embryonic day 9.5 through to postnatal day 21. Low levels of transcripts for Crim1 are first detected in the lens placode. By the lens pit stage, Crim1 is markedly upregulated with high levels persisting throughout embryonic and foetal development. Crim1 is expressed in both lens epithelial and fibre cells. As lens fibres mature in the nucleus, Crim1 is downregulated but strong expression is maintained in the lens epithelium and in the young fibre cells of the lens cortex. Crim1 is also detected in other developing ocular tissues including corneal and conjunctival epithelia, corneal endothelium, retinal pigmented epithelium, ciliary and iridial retinae and ganglion cells. During postnatal development Crim1 expression is restricted to the lens, with strongest expression in the epithelium and in the early differentiating secondary fibres. Thus, strong expression of Crim1 is a distinctive feature of the lens during morphogenesis and postnatal growth.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10466137 20283522
bozozok and squint act in parallel to specify dorsal mesoderm and anterior neuroectoderm in zebrafish.
Sirotkin HI; Dougan ST; Schier AF; Talbot WS
Department of Developmental Biology, Stanford University School of Medicine, Beckman Center B300, Stanford, CA 94305, USA.
Development (ENGLAND) Jun 2000, 127 (12) p2583-92, ISSN 0950-1991
Journal Code: ECW
Contract/Grant No.: F32HD08420, HD, NICHD; GM57825, GM, NIGMS; GM56211, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In vertebrate embryos, maternal (beta)-catenin protein activates the expression of zygotic genes that establish the dorsal axial structures. Among the zygotically acting genes with key roles in the specification of dorsal axial structures are the homeobox gene bozozok (boz) and the nodal-related (TGF-(beta) family) gene squint (sqt). Both genes are expressed in the dorsal yolk syncytial layer, a source of dorsal mesoderm inducing signals, and mutational analysis has indicated that boz and sqt are required for dorsal mesoderm development. Here we examine the regulatory interactions among boz, sqt and a second nodal-related gene, cyclops (cyc). Three lines of evidence indicate that boz and sqt act in parallel to specify dorsal mesoderm and anterior neuroectoderm. First, boz requires sqt function to induce high levels of ectopic dorsal mesoderm, consistent with sqt acting either downstream or in parallel to boz. Second, sqt mRNA is expressed in blastula stage boz mutants, indicating that boz is not essential for activation of sqt transcription, and conversely, boz mRNA is expressed in blastula stage sqt mutants. Third, boz;sqt double mutants have a much more severe phenotype than boz and sqt single mutants. Double mutants consistently lack the anterior **neural** tube and axial mesoderm, and ventral fates are markedly expanded. Expression of **chordin** and noggin1 is greatly reduced in boz;sqt mutants, indicating that the boz and sqt pathways have overlapping roles in activating secreted **BMP** antagonists. In striking contrast to boz;sqt double mutants, anterior **neural** fates are specified in boz;sqt;cyc triple mutants.

This indicates that cyc represses anterior **neural** development, and that boz and sqt counteract this repressive function. Our results support a model in which boz and sqt act in parallel to induce dorsalizing **BMP**-antagonists and to counteract the repressive function of cyc in **neural** patterning.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10463358 20230147
Spatiotemporal expression patterns of mammalian **chordin** during postgastrulation embryogenesis and in postnatal brain.
Scott IC; Steiglitz BM; Clark TG; Pappano WN; Greenspan DS
Department of Pathology and Laboratory Medicine, University of Wisconsin Medical School, Madison, Wisconsin 53706, USA.
Developmental dynamics (UNITED STATES) Apr 2000, 217 (4) p449-56, ISSN 1058-8388 Journal Code: A9U
Contract/Grant No.: AR43621, AR, NIAMS; GM46846, GM, NIGMS; T32GM07215, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Chordin is an antagonist of TGFbeta-like bone morphogenetic proteins (BMPs) that plays roles in dorsoventral axis formation and in induction, maintenance and/or differentiation of **neural** tissue in early vertebrate embryogenesis. In contrast, little is known concerning possible roles for **Chordin** at later stages of vertebrate development and in the adult. To provide insights into possible postgastrulation roles for **Chordin**, we report the spatiotemporal expression patterns of **Chordin** in 8.5- to 15.5-dpc mouse embryos and in the postnatal mouse brain. Expression of **Chordin** in the primordia of most major organs from 10.5 dpc, including the brain, lung, heart, liver, kidney, thymus, and gut, suggests multiple functions for **Chordin** in organogenesis, potentially by means of interactions with TGFbeta-like BMPs. The relatively high levels of **Chordin** expression in condensing and differentiating cartilage elements from 11.5 dpc indicates a generalized role for **Chordin** throughout embryonic skeletogenesis. In the postnatal mouse brain, we demonstrate that **Chordin** is coexpressed with other components of the TGFbeta-like **BMP** signalling pathway in the cerebellum and hippocampus, sites of high synaptic plasticity, suggesting a role for **Chordin** in this process.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10456959 20233835
Processing of the Drosophila Sog protein creates a novel **BMP** inhibitory activity.
Yu K; Srinivasan S; Shimmi O; Biehs B; Rashka KE; Kimelman D; O'Connor MB; Bier E
Department of Biology and Center for Molecular Genetics, University of California, San Diego, La Jolla, California 92093-0349, USA.
Development (ENGLAND) May 2000, 127 (10) p2143-54, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Structurally unrelated **neural** inducers in vertebrate and invertebrate embryos have been proposed to function by binding to BMP4 or Dpp, respectively, and preventing these homologous signals from activating their receptor(s). In this study, we investigate the functions of various forms of the Drosophila Sog protein using the discriminating assay of Drosophila wing development. We find that misexpression of Drosophila Sog,

or its vertebrate counterpart **Chordin** , generates a very limited vein-loss phenotype. This Sog misexpression phenotype is very similar to that of viable mutants of glass-bottom boat (gbb), which encodes a **BMP** family member. Consistent with Sog selectively interfering with Gbb signaling, Sog can block the effect of misexpressing Gbb, but not Dpp in the wing. In contrast to the limited **BMP** inhibitory activity of Sog, we have identified carboxy-truncated forms of Sog, referred to as Supersog, which when misexpressed cause a broad range of dpp(-) mutant phenotypes. In line with its phenotypic effects, Supersog can block the effects of both misexpressing Dpp and Gbb in the wing. Vertebrate **Noggin** , on the other hand, acts as a general inhibitor of Dpp signaling, which can interfere with the effect of overexpressing Dpp, but not Gbb. We present evidence that Sog processing occurs in vivo and is biologically relevant. Overexpression of intact Sog in embryos and adult wing primordia leads to the developmentally regulated processing of Sog. This in vivo processing of Sog can be duplicated in vitro by treating Sog with a combination of the metalloprotease Tolloid (Tld) plus Twisted Gastrulation (Tsg), another extracellular factor involved in Dpp signaling. In accord with this result, coexpression of intact Sog and Tsg in developing wings generates a phenotype very similar to that of Supersog. Finally, we provide evidence that tsg functions in the embryo to generate a Supersog-like activity, since Supersog can partially rescue tsg(-) mutants. Consistent with this finding, sog(-)and tsg(-) mutants exhibit similar dorsal patterning defects during early gastrulation. These results indicate that differential processing of Sog generates a novel **BMP** inhibitory activity during development and, more generally, that **BMP** antagonists play distinct roles in regulating the quality as well as the magnitude of **BMP** signaling.

5/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10421369 20193497

Coincidence of otx2 and BMP4 signaling correlates with Xenopus cement gland formation.

Gammill LS; Sive H
Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, USA.

Mechanisms of development (IRELAND) Apr 2000, 92 (2) p217-26, ISSN 0925-4773 Journal Code: AXF
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We previously showed that otx2 activates ectopic formation of the Xenopus cement gland only in ventrolateral ectoderm, defining a region of the embryo permissive for cement gland formation. In this paper, we explore the molecular identity of this permissive area. One candidate permissive factor is BMP4, whose putative graded inhibition by factors such as **noggin** has been proposed to activate both cement gland and **neural** fates. Several lines of evidence are presented to suggest that **BMP** signaling and otx2 work together to activate cement gland formation. First, BMP4 is highly expressed in the cement gland primordium together with otx2. Second, cement gland formation in isolated ectoderm is always accompanied by coexpression of otx2 and BMP4 RNA, whether cement gland is induced by otx2 or by the **BMP** protein inhibitor **noggin**. Third, **BMP** signaling can modulate otx2 activity, such that increasing **BMP** signaling preferentially inhibits **neural** induction by otx2, while decreasing **BMP** signaling prevents cement gland formation. In addition, we show that a hormone-inducible otx2 activates both ectopic **neural** and cement gland formation within the cement gland permissive region, in a pattern reminiscent of that found in the embryo. We discuss this observation in view of a model that BMP4 and otx2 work together to promote cement gland formation.

5/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10374651 20200132
Characterization of the functionally related sites in the **neural** inducing gene **noggin**.
Liu W; Ren C; Shi J; Feng X; He Z; Xu L; Lan K; Xie L; Peng Y; Fan J; Kung Hf; Yao KT; Xu RH
Cancer Research Institute, Hunan Medical University, Changsha, Hunan, 410078, China.
Biochemical and biophysical research communications (UNITED STATES) Apr 2 2000, 270 (1) p293-7, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previously we have shown that blocking bone morphogenetic protein (**BMP**) receptor signaling by a dominant negative **BMP** receptor causes neurogenesis in Xenopus animal caps (ACs), whereas the physiological **neural** inducer **noggin** acts as a homodimer physically binding to **BMP** -4 and disrupting its signaling at the ligand level. The present study attempted to elucidate the relationship between the structure and function of **noggin**. By replacing some cysteine residues with serine residues through a site-directed mutagenesis strategy, we generated three **noggin** mutants, C145S, C205S, and C(218, 220, 222)S (3CS). Although mRNAs encoded by these mutants were translated as efficiently as wild-type (WT) **noggin** mRNA, they behaved differently when expressed in vivo. Expression of WT **noggin** or C205S in Xenopus ACs converted the explants (prospective ectoderm) into **neural** tissue, indicated by the **neural**-like morphology and expression of the pan **neural** marker NCAM in the ACs. In contrast, ACs expressing C145S or 3CS sustained an epidermal fate like the control caps. Similar results were observed in the mesoderm where C205S (but not C145S and 3CS) displayed dorsalizing activity as well as WT **noggin**. Altogether, our results suggest that Cys145 alone or Cys(218, 220, 222) as a whole in **noggin** protein is required for the biological activities of **noggin**, probably participating in the dimerization of **noggin** with **BMP**-4 or itself. Copyright 2000 Academic Press.

5/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10344875 20125902
Developmental changes in progenitor cell responsiveness to bone morphogenetic proteins differentially modulate progressive CNS lineage fate.
Mehler MF; Mabie PC; Zhu G; Gokhan S; Kessler JA
Department of Neurology, the Rose F. Kennedy Center for Research in Mental Retardation and Developmental Disabilities, Albert Einstein College of Medicine, Bronx, N.Y., USA. mehler@aecom.yu.edu
Developmental neuroscience (SWITZERLAND) 2000, 22 (1-2) p74-85, ISSN 0378-5866 Journal Code: EC5
Contract/Grant No.: NS35320, NS, NINDS; NS38902, NS, NINDS; NS20013, NS, NINDS; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Although multipotent progenitor cells capable of generating neurons, astrocytes and oligodendrocytes are present within the germinal zones of the brain throughout embryonic, postnatal and adult life, the different **neural** cell types are generated within discrete temporospatial developmental windows. This might suggest that multipotent progenitor cells encounter different signals during each developmental stage, thus accounting for separate waves of lineage commitment and cellular

differentiation. This study demonstrates, however, that progenitor cell responses to the same [redacted]ss of signals, the bone morpho[redacted]etic proteins (BMPs), change during ontogeny, and that these same signals may thus initiate progenitor cell elaboration of several different lineages. BMPs promote cell death and inhibit the proliferation of early (embryonic day 13, E13) ventricular zone progenitor cells. At later embryonic (E16) stages of cerebral cortical development, BMPs exhibit a concentration-dependent dissociation of cellular actions, with either enhancement of neuronal and astroglial elaboration (at 1-10 ng/ml) or potentiation of cell death (at 100 ng/ml). Finally, during the period of perinatal cortical gliogenesis, BMPs enhance astroglial lineage elaboration. By contrast, oligodendroglial lineage elaboration is inhibited by the BMPs at all stages. Further, application of the **BMP** antagonist **noggin** to cultured progenitors promotes the generation of oligodendrocytes, indicating that endogenous **BMP** signaling can actively suppress oligodendrogliogenesis. These observations suggest that developmental changes in **neural** progenitor cell responsiveness to the BMPs may represent a novel mechanism for orchestrating context-specific cellular events such as lineage elaboration and cellular viability. Copyright 2000 S. Karger AG, Basel.

5/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10336201 20129932
BMP signaling is essential for development of skeletogenic and neurogenic cranial **neural** crest.
Kanzler B; Foreman RK; Labosky PA; Mallo M
Max-Planck Institute of Immunobiology, Stubeweg 51, D-79108 Freiburg, Germany.
Development (ENGLAND) Mar 2000, 127 (5) p1095-104, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BMP signaling is essential for a wide variety of developmental processes. To evaluate the role of Bmp2/4 in cranial **neural** crest (CNC) formation or differentiation after its migration into the branchial arches, we used Xnoggin to block their activities in specific areas of the CNC in transgenic mice. This resulted in depletion of CNC cells from the targeted areas. As a consequence, the branchial arches normally populated by the affected **neural** crest cells were hypomorphic and their skeletal and **neural** derivatives failed to develop. In further analyses, we have identified Bmp2 as the factor required for production of migratory cranial **neural** crest. Its spatial and temporal expression patterns mirror CNC emergence and Bmp2 mutant embryos lack both branchial arches and detectable migratory CNC cells. Our results provide functional evidence for an essential role of **BMP** signaling in CNC development.

5/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10320594 20183256
Noggin expression in a mesodermal pluripotent cell line C1 and its regulation by **BMP**.
Nifuji A; Kellermann O; Noda M
Department of Molecular Pharmacology, Medical Research Institute, Tokyo Medical and Dental University, Japan.
Journal of cellular biochemistry (UNITED STATES) Jun 15 1999, 73 (4) p437-44, ISSN 0730-2312 Journal Code: HNF
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Osteoblasts and chondrocytes are derived from mesodermal stem cells and their differentiation is under the control of coordinated interaction among signaling molecules. **Noggin** is one of the signaling molecules which bind to and inactivate BMPs to induce **neural** tissues and dorsal mesoderm in Xenopus. However, its expression and regulation in mammalian cells has not been known. In this study, we investigated expression of **noggin** in murine pluripotent mesodermal cell line, C1. **Noggin** expression was very low in these C1 cells before they were induced to differentiate. When C1 cells were induced to differentiate into chondrocytes in aggregate cultures in the presence of dexamethasone(dex), **noggin** expression was significantly increased. In a sharp contrast, when the C1 cells were induced to differentiate into osteoblastic cells by the treatment with beta glycerophosphate (betaGP) and ascorbic acid (AA), **noggin** mRNA expression remained to be barely detectable. **Noggin** expression was also observed in the developing cartilage of vertebrae in 15.5 dpc mouse embryos. The **noggin** mRNA level in C1 cells in monolayer cultures was enhanced significantly by the treatment with BMP4/7 in a dose-dependent manner with a maximal effect at 100 ng/ml. The BMP4/7 effect on **noggin** expression was time dependent starting within 12 h and peaked at 24 h. These results indicate that **noggin** is expressed in the pluripotent mesodermal cell line C1 and that its expression is regulated by **BMP**.

5/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10308118 99425167

Direct regulation of the Xenopus engrailed-2 promoter by the Wnt signaling pathway, and a molecular screen for Wnt-responsive genes, confirm a role for Wnt signaling during **neural** patterning in Xenopus.

McGrew LL; Takemaru K; Bates R; Moon RT

Howard Hughes Medical Institute, Department of Pharmacology and Center for Developmental Biology, University of Washington School of Medicine, Seattle, WA 98195, USA.

Mechanisms of development (IRELAND) Sep 1999, 87 (1-2) p21-32, ISSN 0925-4773 Journal Code: AXF

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The co-activation of Wnt signaling and concomitant inhibition of **BMP** signaling has previously been implicated in vertebrate **neural** patterning, as evidenced by the combinatorial induction of engrailed-2 and krox-20 in Xenopus. However, screens have not previously been conducted to identify additional potential target genes. Using a PCR-based screening method we determined that XA-1, xCRISP, UVS.2, two UVS.2-related genes, and xONR1 are induced in response to Xwnt-3a and a **BMP**-antagonist, **noggin** . Two additional genes, connexin 30 and retinoic acid receptor gamma were induced by Xwnt-3a alone. To determine whether any of the induced genes are direct targets of Wnt signaling, we focussed on engrailed-2. In the present study we show that the Xenopus engrailed-2 promoter contains three consensus binding sites for LEF/TCF, which are HMG box transcription factors which bind to beta-catenin in response to activation of the Wnt- 1 signaling pathway. An engrailed-2 promoter luciferase reporter construct containing these LEF/TCF sites is induced in embryo explant assays by the combination of Xwnt-3a or beta-catenin and **noggin** . These LEF/TCF sites are required for expression of engrailed-2, as a dominant negative Xtcf-3 blocks expression of endogenous engrailed-2 as well as expression of the reporter construct. Moreover, mutation of these three LEF/TCF sites abrogates expression of the reporter construct in response to **noggin** and Xwnt-3a or beta-catenin. We conclude that the engrailed-2 gene is a direct target of the Wnt signaling pathway, and that Wnt signaling works with **BMP** antagonists to regulate gene expression during patterning of the developing nervous system of Xenopus.

5/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10300917 20003245
A role for the extraembryonic yolk syncytial layer in patterning the zebrafish embryo suggested by properties of the hex gene.
Ho CY; Houart C; Wilson SW; Stainier DY
Department of Biochemistry and Biophysics University of California at San Francisco San Francisco, California, 94143-0448, USA.
Current biology (ENGLAND) Oct 7 1999, 9 (19) p1131-4, ISSN 0960-9822 Journal Code: B44
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recent studies in mouse suggest that the extraembryonic endoderm has an important role in early embryonic patterning [1]. To analyze whether similar mechanisms operate in other vertebrates, we cloned the zebrafish homologue of Hex, a homeobox gene that is expressed asymmetrically in the mouse visceral endoderm [2]. Early expression of zebrafish hex is restricted to the dorsal portion of the yolk syncytial layer (YSL), an extraembryonic tissue. By the onset of gastrulation, hex is expressed in the entire dorsal half of the YSL, which directly underlies the cells fated to form the **neural** plate. We show that hex expression is initially regulated by the maternal Wnt pathway and later by a **Bmp**-mediated pathway. Overexpression experiments of wild-type and chimeric Hex constructs indicate that Hex functions as a transcriptional repressor and its overexpression led to the downregulation of bmp2b and wnt8 expression and the expansion of **chordin** expression. These findings provide further evidence that the zebrafish YSL is the functional equivalent of the mouse visceral endoderm and that extraembryonic structures may regulate early embryonic patterning in many vertebrates.

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Bone morphogenetic proteins are required in vivo for the generation of sympathetic neurons.
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Bone morphogenetic proteins (BMPs) induce autonomic neurogenesis in **neural** crest cultures and stimulate sympathetic **neuron** development when overexpressed in vivo. We demonstrate that inhibition of BMPs in the chick embryo bythe **BMP** antagonist **Noggin** prevents sympathetic **neuron** generation. In **Noggin**-treated embryos, the noradrenergic marker genes tyrosine hydroxylase (TH) and dopamine-beta-hydroxylase (DBH), panneuronal neurofilament 160 (NF160) and SCG10 genes, and the transcriptional regulators Phox2b and Phox2a are not expressed in sympathetic ganglia. Whereas initial ganglion development is not affected, the expression of the basic helix-loop-helix transcription factor Cash-1 is strongly reduced. These results demonstrate that BMPs are essential for sympathetic **neuron** development and establish Cash-1 and Phox2 genes as downstream effectors of BMPs in this lineage.

5/3,AB/13 (Item 13 from file: 155)